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Proposed Guidelines

for

Good Epidemiological Practice

_____ 1994

SECTION I: INTRODUCTION (GENERAL PROVISIONS)

Should guidelines and standards be used synonymously?

PREFACE

Historically, epidemiology has proven to be a useful tool for exploring potential relationships between human health and environmental exposures. Over time, the focus has shifted from acute infections and dietary diseases to chronic disorders that are the principal causes of death in industrialized society. Currently, the scope of epidemiological research continues to expand. Not only have epidemiological results been adopted by a widening circle of countries but the enhanced potential for the collection, storage and analysis of data, offered by advances in information technology, have made it possible to examine an increasing number of relationships between populations and disease with greater precision. Further, the use of experimental data in an epidemiological framework has also increased the application of epidemiology to other scientific disciplines. National and international bodies now routinely use epidemiological findings, in combination with toxicological research, as a scientific basis for risk assessment. Many now formulate public health policy, regulations and legislation on the outcome of such research.

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how is this defined

Whereas rigorous and uniform standards exist for the conduct of experimental studies, no comparable guidelines govern epidemiological research. Specific criteria for the design, conduct, documentation, analysis and reporting of studies should strengthen epidemiological

Defined

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research overall. The resulting uniformity ~~of approach~~ would assist in ~~the~~ combining of data and ~~the~~ comparison ~~of~~ outcomes. Duplicative testing could be avoided, introducing ~~economies in cost and time~~. Guidelines would also be useful in training those new to the field as well as practitioners from other disciplines seeking to apply epidemiological techniques. A set of standards would bolster public confidence in the reliability of epidemiological results and assist regulators in responding to critics of public health policies based on research conducted in accordance with sound epidemiological practices.

As a consequence THE EXECUTIVE COMMITTEE OF _____ proposes to establish the following guidelines for Good Epidemiological Practice (GEP).

[History and credentials of the committee and its activities:

The draft was prepared by a task force group whose members are experienced occupational and environmental epidemiology practitioners, who conduct research within the academic and industrial setting. ....]

The GEPs propose minimum practice and procedural standards to assist researchers in ensuring the quality and integrity of data used in epidemiological research and to provide adequate documentation of methods and results. While GEP guidelines will not guarantee good epidemiology, they will provide a framework within which sound science can be conducted.

Goals

The purpose of these guidelines of GEP is:

- to promote sound epidemiological research by encouraging well justified design, quality data collection, thorough analysis as well as comprehensive documentation;
- to maintain scientific objectivity;

- to provide a framework to assist researchers in adhering to good epidemiological principles;
- to improve the utility of epidemiological studies in the formulation of public policy;
- to maintain public confidence in epidemiology as a scientific discipline;
- to make optimal use of research resources;
- to assist training in the use of epidemiological techniques.

Related declarations and guidelines

A number of organizations have proposed guidelines for epidemiological research:

The **World Health Organization** (WHO) published guidelines on studies in environmental epidemiology (Envir. Health. Criteria 27, Geneva, 1983).

In this context also the *Good Clinical Practices* for Trials on Medicinal Products in the **European Community** (GCP) (EG-GCP-Note for Guidance, 1991) are relevant.

The **Environmental Protection Agency** (EPA) modified both the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Toxic Substances Control Act (TSCA) *Good Laboratory Practice Standards* (GLPs)[1] to specifically include epidemiology (54 CFR 34034) (August 17, 1989).

The **National Research Council** in its Redbook II: "Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food," US Food and

[1] The GLP's are directed primarily at experimental laboratory research, often involving the use of animals or cell culture systems. The GLPs address issues that confront researchers conducting experimental toxicological research.

from the study plan to the final report/publication.

Standard Operating Procedure (SOP) - any written standard method or process for conducting or accomplishing a routine research procedure not unique to a specific study.

Study - epidemiological research relating to the distribution and determinants of health-related outcomes in specified populations.

Study plan - document prepared prior to the start of the collection of study data, which states the organization, aims, and methods of the research.

Study review - critical evaluation of a scientific study or investigation at any stage of development by peers of the principal investigator.

SECTION II: GOOD EPIDEMIOLOGICAL PRACTICE GUIDELINES

1. Organizational Structure

The responsibilities, relationship, and roles of the individuals and organizations designing, conducting and funding the study and, in particular, the ownership of the study data and the responsibility for document archiving should be carefully defined in writing.

2. Qualification and Responsibilities of Study Researchers

Personnel:

Personnel engaged in epidemiological studies and related activities shall have the education, training, and/or experience necessary competently to perform assigned functions including compliance with the GEPs.

- measurement instrument validation studies;
- cross-sectional studies (surveys);
- prospective studies (cohort or follow-up);
- retrospective studies (case-control studies).

Experimental studies, including clinical trials, case reports, methodological studies etc., do not fall within the scope of these guidelines.

Meta-analytic techniques, data pooling and other procedures for combining data in a systematic review of pre-existing literature or in a multi-center approach to studying a single issue would be within the scope of the GEPs.

FURTHER DEVELOPMENT

The current document is an initial step in developing a framework for improving epidemiological research practices through adherence to sound scientific research principles. The guidelines emphasize data integrity and adequate documentation of study methods. It is anticipated that these guidelines will evolve based on experience gained through their application.

DEFINITION OF TERMS

Principal investigator - the research investigator who has direct responsibility for the design, conduct, analysis, and interpretation of a specific study or investigation.

Quality assurance - the overall program that ensures conformance to established performance standards. The quality assurance process encompasses all aspects of the research operation

Drug Administration, Center for Food Safety and Applied Nutrition, 1993, refers to "Guidelines for Documentation of Epidemiological Studies", published by the Epidemiology Work Group of the Interagency Regulatory Liaison Group in November 1981, in the American Journal of Epidemiology.

The Chemical Manufacturers' Association's Epidemiology Task Group developed guidelines for good epidemiology practices for occupational and environmental epidemiological research (J. Occ. Med. 33: 1221-1229 (1991)), which were used as a model for the present document. These

None of these are binding for researchers or administrators using data from epidemiological studies for public health policies.

The ethical aspects of epidemiological studies are covered by international guidelines (e.g., World Health Organization: International Ethical guidelines for Biomedical Research involving Human Subjects, Council for International Organizations for Medical Sciences, Geneva, 1993).

SCOPE AND APPLICATION

The GEP guidelines should be applied to all types of non-experimental, occupational and environmental epidemiological research worldwide. They are applicable to research conducted or sponsored by industry or governmental agencies as well as for research at universities or equivalent institutions.

GEPs should encompass all activities that begin with the development of a study plan. Adherence to the spirit of the guidelines will be beneficial for those activities preceding the development of a study plan as well as more informal investigations such as health hazard assessment/ evaluations or small cluster investigations.

GEPs would specifically pertain to all analytical studies such as:

The principal investigator or the organization conducting the research shall maintain documents proving the appropriate training and experience of all personnel engaged in the study. Job descriptions for each individual engaged in or supervising activities are encouraged.

Principal investigator (/Study director/):

The principal investigator shall be responsible for the individual research project including day-to-day conduct of the study, interpretation of study data and preparation of the final report. His or her responsibilities extend to all aspects of the study including periodic reporting of study progress as well as quality assurance.

. qualifications, substitution

Collaborators:

number, qualifications, substitution

Special care should be given to the training and monitoring of those administering questionnaires and surveys; blinded techniques are preferred.

3. Facilities and Resources

Adequate physical facilities (e.g., space, equipment, and supplies) shall be available to those engaged in epidemiological research to ensure timely completion of all studies. Suitable storage facilities shall be available to maintain research materials and data in a safe and secure environment.

4. Study Plan

Each project shall have a written study plan that has been approved before the study begins.

The study plan should include:

A. A descriptive title.

B. The names, titles, degrees, addresses, and affiliations of the principal investigator and all co-investigators.

C. The names and addresses of the sponsors or funding agencies.

D. An abstract.

E. A timetable including study approval date (date supply plan signed by all signatories), study start date (first date that the study plan is implemented), periodic progress review dates, and completion date.

F. A statement of all research hypotheses, objectives, specific aims, and rationale.

This statement should identify the immediate purpose of the investigation. For example, it might also indicate whether the study will include exploratory data analysis, hypothesis testing, or a combination of both as well as whether the proposed study will address previously unanswered questions, will attempt to corroborate or confirm previous findings, or will be routine epidemiological surveillance.

G. A review of all relevant literature.

For example, the literature review should encompass animal and human experiments, clinical studies, vital statistics, and previous epidemiological studies. The literature review should be of sufficient depth to identify potential confounders and effect modifiers and to determine areas where new knowledge

is needed.

H. A description of research methods, including:

1. The overall research design and strategy and reasons for choosing the proposed study design.

   For example, case-control, cohort, cross-sectional, nested case-control, or other hybrid designs.

   In case-control studies, special attention should be given to how the control group will be selected and what matching procedures will be utilized. Also, case selection should be explained with an emphasis on efforts to ensure a high participation rate.

2. The data sources for exposure, health status, and risk factors.

   For example, questionnaires, biological measurements, exposure/work history record reviews, or exposure/disease registries.

3. Clearly designed parameters for health outcomes, exposure, and measured risk factors including selection criteria, when appropriate for exposed and nonexposed persons, morbidity or mortality cases, the referent groups.

4. Projected study size and, if appropriate, statistical power.

   This should include underlying assumptions for distribution, variance, correlation, and regression procedures. The degree to which violation of these assumptions could invalidate the analysis should be specified whenever possible.

   Meta-analysis and pooling techniques are best used for homogenous

data gather under a uniform protocol.

5. Methods for assembling study data.

This should include a description of methods used to control, measure, or reduce various forms of error -- e.g., bias due to limited response rate, selection, misclassification, interviewer, or confounders -- and their possible impact on the study. Pretesting procedures for research instruments and any manuals or formal training to be provided to interviewers, abstractors, coders, or data entry personnel should be described and referenced.

6. Methods for data analysis.

This should include a description of procedures for defining or categorizing exposure and health outcome variables for purposes of analysis. It should also include provisions for assessing dose-response relationships and treatment of potentially confounding and effect modifying variables. This should also include procedures to control, if possible, sources of bias and their influence on results and a description of planned comparisons and statistical methods for analyzing and presenting results.

7. Major limitations of the study design, data sources, and analytic methods.

This should include a description and acknowledgment of the limiting parameters inherent in the study size, approach, available data and methodology with specific emphasis on permissible conclusions to be drawn from possible outcomes.

8. Criteria for interpreting study results.

This should include a brief discussion of the characteristics of the proposed study design, including limitations that will influence the discussion of the results. It should state, for example, that statistically significant associations do not in themselves provide direct evidence of a causal relationship and that causation can only be established on non-statistical grounds. The statistical tests to be applied to the data should be specified and procedures for obtaining point estimates and confidence intervals for measures of occurrence or associations should also be described. Generally, 95% confidence intervals are preferred.

I. A plan for the protection of human subjects.

This should include information about whether study subjects will be placed at risk as a result of the study, under what circumstances informed consent will be required, and provisions for maintaining confidentiality of information on study subjects.

J. A description of quality control procedures for all phases of the study including, when appropriate, the certification and/or qualifications of any supporting laboratory or research groups.

K. The bibliographic references.

L. Addenda, as appropriate.

For example, correspondence, collaborative agreements, institutional approvals, and samples of the informed consent forms, questionnaires, and representative samples of other documents to be used in the study.

M. A dated study plan review and approval sign-off sheet.

N. Dated amendments to the study plan.

5. Review and Approval

A review of study plans and the final report should encompass all aspects of the study as outlined in the Guidelines for Good Epidemiological Practice, Section 4: Study Plan and Section 6: Study Conduct.

A. Scientific Review

The study plan shall be reviewed by qualified personnel, who are not part of the investigative team, to ensure that the design addresses the objectives of the research and that the study plan is written according to the Guidelines for Good Epidemiological Practice. The nature and circumstances of this review shall be documented.

The scientific aspects of the completed study shall receive appropriate technical review to ensure that the abstract, summary, and conclusions are supported by the underlying data, methods, and analyses. The nature and circumstances of this review shall be documented.

B. Ethical Review

The ethical aspects of each study plan shall be reviewed by an institutional review board or other comparable review procedure.

This review should consider:

1. Obligations to research subjects;

For example, protecting the welfare of study subjects by maintaining the privacy and confidentiality of communications and operating within the requirements of informal consent.

2. Obligations to society;

For example, avoiding conflicts of interest and partiality; appropriately disseminating study findings and open sharing while generally pursuing research responsibilities with due diligence.

3. Obligations to funding institutions and employers.

For example, specifying obligations in contractual form of how research is to be conducted and how it may involve ethical, technical, administrative, or legal responsibilities; presenting methods and alternatives; and protecting privileged information.

For example, promoting and preserving public confidence in epidemiological research while not over- or underestimating the methods or results of epidemiological inquiry; reporting methods and results; and disseminating the study's findings.

C. Administrative Review

The administrative aspects of the study plan shall receive appropriate review and written approval by sponsors, contractors, and associated third parties to ensure sufficient resources are available to complete the study in a timely and proper fashion.

Reports shall include a statement that the study was completed in accordance with the study plan, including any approved modifications to the study plan, and in accordance with the GEPs. Any deviations from the GEPs shall be explained and documented.

6. Study Conduct

To ensure the proper conduct of the study, personnel shall adhere to sound research principles and practices established according to the study plan.

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A study plan may be approved before the study begins. Research shall be conducted in accordance with the study plan; all deviations (e.g., errors in randomization, low participation rate, additional confounders) from the study plan shall be properly explained and documented in a written supplement to the study plan and authorized by the principle investigator. Implications for the study's reliability and consistency shall be evaluated and described.

If a decision is made not to complete a research project, the reasons for that decision shall be put in writing, dated, and signed by the responsible party (i.e., the individual who makes the decision to terminate the study) and communicated to the funding authority whenever possible.

A. Protection of Human Subjects

Procedures for protecting human subjects shall be followed. Confidential information about study subjects shall be protected using established procedures.

If stipulated by the study plan and/or required by an institutional review board, each participant shall be informed about the purpose of the study and any risks associated with the study. Written consent, if required, shall be obtained from each subject before he or she participates.

Written consent shall at a minimum include:

1. Purpose of the research.

2. Names, addresses, and phone numbers of personnel available to answer questions about the research and the rights of study subjects.

3. Expected duration of participation.

4. Eligibility requirements for study (s) / to the study subject or others

5. Possible benefits from study results.

6. Statement on the voluntary nature of participation in the study and the right of every study subject to discontinue participation at any time.

7. Statement of confidentiality of records identifying the study subject, including reasonable exceptions to absolute confidentiality (e.g., sharing of information with the study subject's personal physician or as required by court order).

8. Description of any foreseeable risks or discomforts to the study subject.

9. Statement of availability of results.

B. Data Collection and Verification

All data collected for the study should be recorded accurately and as promptly as possible. The individuals responsible for data integrity, both computerized and hard copy, shall be identified.

All procedures used to verify and promote the quality and integrity of the data shall be outlined in writing. A historical file of these procedures shall be maintained, including all revisions and the dates of such revisions. Any changes in data entries shall be documented.

C. Analysis

All data management and statistical programs used in the analyses should be documented. All dated versions used in the research shall be kept with accompanying documentation.

If the data is not supportive of the stated hypotheses, no further analysis is necessary. Subsequent treatment of the data should only be for hypothesis generating purposes. Odds ratios of 2 or less should be treated with caution, particularly when the confidence intervals are wide. There is a likelihood that the odds ratio is the result of problems with case or control selection, confounders or bias.

D. Study Report or Publication(s)

Completed studies shall be summarized in a final report and/or publications in scientific journals that accurately and completely present the study objectives, methods, results, and the principal investigator's interpretation of the findings. Rigorous scientific objectivity should be the standard for reporting results. Limitations in study design, conduct, and analysis should be stated.

The final report/publication shall include at a minimum:

1. A descriptive title.

2. An abstract.

3. The purpose (objectives) of the research as stated in the study plan.

4. The names, titles, degrees, addresses, and affiliations of the principal investigator and all co-investigators.

5. All names and addresses of sponsors.

6. The dates on which the study was initiated and completed.

7. An introduction with background, purpose, hypothesis and specific aims of the study.

8. A description of the research methods, including:

   a. the selection of study subjects and controls;

   b. the data collection methods used;

   c. the transformations, calculations, or operations on the data, and

   d. statistical methods used in data analyses.

9. A description of circumstances that may have affected the quality or integrity of the data including an assessment of both the range and distribution of predicted values (variance) and the effect of untested assumptions on the central tendency of the distribution of predicted values (bias).

10. A summary and analyses of the data.

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Include sufficient tables, graphs, and illustrations to present the pertinent data and to reflect the analyses performed.

An adequate description of the raw data should precede and complement formal statistical analysis.

Graphic display of results and figures that show individual observations are to be encouraged. For example, when appropriate, fitted regression lines should be presented together with a scatter diagram of the raw data. Any complex statistical method should be communicated in a manner that is comprehensible to the reader.

11. A statement of the conclusions drawn from the analyses of the data.

12. A discussion of the implication of study results.

Cite prior research in support of and in contrast to present findings. Discuss possible biases and limitations in present research.

13. References.

14. A statement describing the location where all source data and the final report are stored. Raw data should be made available upon request to all interested investigators.

15. A dated study report review sign-off sheet of the principal investigator, co-investigators, and reviewers and/or auditors (for reports only).

7. Communication

Scientific peers shall be informed of study results by publication in scientific literature or presentations at scientific conferences, workshops, or symposia. To reduce publication bias, every effort should be made to publish and report on all completed research, regardless of outcome.

8. Archiving

There shall be physically secure archives for the orderly storage and expedient retrieval of all study related material. An index shall be prepared to identify the archived contents, to identify their location, and to identify by name and location any materials that by their general nature are not retained in the study archive.

Access to the archives shall be controlled and limited to authorized personnel only. Special procedures may be necessary to ensure that access to confidential information is limited and that the confidentiality of information about study subjects is protected.

At a minimum, the study archive should contain, or refer to, the following:

A. Study plan and copies of all approved modifications.

B. A final report or publication of the study.

C. All source data and, where feasible, specimens. A printed sample of the master computer data file with reference to the location of the machine readable master.

If the data include employee medical records, subject to local regulation, the records shall be retained according to the provisions of those regulations.

D. Documentation shall be adequate to identify and locate all computer programs and statistical procedures used, including version numbers where appropriate.

E. Copies of computer printouts, including relevant execution code, that form the basis of any tables, graphs, discussions, or interpretations in the final report shall be preserved. Any manually developed calculations shall be documented on a work sheet and similarly retained.

F. Correspondence pertaining to the study, standard operating procedures, informed consent releases, copies of all relevant representative material, copies of signed institutional review board and other external reviewer reports, and copies of all quality assurance reports and audits will be appropriately archived.

This includes, for example, sample questionnaires; name, make and model numbers of relevant measurement instruments; calibration information and procedures.

G. Original documents for the following research materials shall be included in the archives:

1. Laboratory/research notebooks.

2. Coder modification notebooks.

3. Signed and dated copies of the study plan and final report.

9. Quality Assurance

Written procedures shall be established to ensure the quality of the data used in the study. These procedures shall address data collection and completeness; coding and computer input, storage and retrieval, as well as data validation and analysis. Any deviations from the GEPs shall be explained and documented.

An individual who is not part of the investigative team should be assigned as a study quality assurance auditor. This individual shall, no less than annually, review study compliance with the written quality assurance procedures., The study quality assurance auditor shall prepare a written summary of the audit. The principal investigator should respond in writing to the audit report, including any remedial actions taken.

Quality assurance activities shall address the preceding sections of these guidelines as well as monitor ~~conformance~~ conformity with established standard operating procedures (SOPs).

10. Standard Operating Procedures

The Guidelines for Good Epidemiology Practices address the conduct of epidemiological studies rather than the management of epidemiological research programs. Many of the suggested guideline requirements can be fulfilled by reference to standard operating procedures for the research program.

Standard operating procedures (SOPs) are written detailed descriptions of routine procedures involved in performing epidemiological studies. Reproducibility, accuracy, and validity are ensured when SOPs are designed to clearly reflect each facility's research procedures. It

should be the responsibility of a designated individual to develop and continuously review and update SOPs pertaining to his area of responsibility. Signatures of approval from the department's managing personnel or appropriate designees should be obtained for all new and updated versions. Significant changes in established SOPs should be maintained, including all versions and the dates of such revisions. The manual of SOPs should be readily available to all research and administrative personnel.

Standard operating procedures should include:

1. A statement of the purpose of the standard operating procedure.
2. A detailed description of the procedure.
3. The person responsible or the training level required to perform the procedure.
4. The date of issue (effective date).
5. the issue number/revision number.
6. Signature of preparer.
7. Authorizing/reviewing signature of management.

Examples of research program activities for which SOPs could be established include:

1. Procedures for collecting raw data.
2. Procedures for validating the completeness of the study population.
3. Procedures for coding death certificates.
4. Procedures for assessing error rates in data abstraction and coding.

5. Security procedures for ensuring the integrity of the raw data and computer records.

6. Procedures for archive management.

7. Procedures for standard industrial hygiene sampling and analytic methods.

8. Procedures for scientific review.

9. Required composition of scientific review boards.

10. Procedures for data analysis.

11. Procedures for communications.